Importance of Early Sepsis Diagnosis for Clinical Care and Patient Outcomes

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Clinical Professor, Wayne State University
Detroit, Michigan
• No competing interests
• Thank you:
  – National Academies
  – Gordon and Betty Moore Foundation
  – Planning Committee
The Early Pathogenesis of Sepsis
Increased Metabolic Demands: Fever, Tachypnea

Microvascular Alterations: Impaired Tissue Oxygen Utilization

Oxygen Demand

Infectious Insult

Hypovolemia, Vasodilation & Myocardial Depression

Oxygen Delivery

Global Tissue Hypoxia

Oxygen Balance

Decreased Oxygen Delivery

DO₁, VO₂, Lactate

Organ Dysfunction and Increased Mortality

Generalized Inflammation

Systemic inflammatory response syndrome: An alternative to septic syndrome

Hemodynamic and Inflammatory Phenotypes

Lactate > 4 mM/L
- 28%

Low ScvO₂
- 23%

Hypotension
- 28%

46%

56%

51%
Risk Stratification

5-10%
10-20%
20-30%
30-50%

Hemodynamic and Inflammatory Phenotypes: Source of Heterogeneity

SIRS
Sepsis
Severe Sepsis
Septic Shock
Why Expand The Diagnostic and Therapeutic Landscape of Sepsis Care?

Going to the disease instead of waiting for it to come to you
The number of ED visits between 2013 and 2016 increased 2.3 million per year.

145 million visits/year (1.7 million with sepsis)
The Reality of Early Sepsis Care: Location Matters

Pre-Hospital or Transfers

General IPD Floors and Post Op

ED

50%

ICU
# Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: a prospective cohort study


<table>
<thead>
<tr>
<th></th>
<th>USA</th>
<th>Europe</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital mortality if origin is emergency department</td>
<td>3008 (24.6%)</td>
<td>736 (34.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hospital mortality if origin is ward</td>
<td>1661 (34.9%)</td>
<td>1481 (43.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hospital mortality if origin is ICU</td>
<td>644 (36.1%)</td>
<td>502 (48.0%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Lancet Infect Dis 2012; 12: 919–24*
The Landscape of Early Sepsis Care in 1997
The Landscape of Early Sepsis Care -1997

- No SIRS criteria
- No risk stratification
  - No Lactate
- No antibiotic recommendations
- No quality assurance measures
- No Surviving Sepsis Campaign
- No CMS measure

- No resuscitation standards:
  - No fluid therapy recommendations
  - No MAP endpoints
  - No recognition of myocardial dysfunction
  - No reassessment standards
<table>
<thead>
<tr>
<th>Condition</th>
<th>Cases/year</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>591,996</td>
<td>6-7</td>
</tr>
<tr>
<td>AMI</td>
<td>540,891</td>
<td>10</td>
</tr>
<tr>
<td>Trauma</td>
<td>697,025</td>
<td>5-16</td>
</tr>
<tr>
<td>Sepsis</td>
<td>859,858</td>
<td>15-20</td>
</tr>
<tr>
<td>Severe Sepsis</td>
<td>791,000</td>
<td>27-40</td>
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<tr>
<td>Septic Shock</td>
<td>200,000</td>
<td>36-47</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1,187,180</td>
<td>5-9</td>
</tr>
</tbody>
</table>
Critical Care is not a location, it is a process. It takes place not only in the ICU but everywhere.”

Dr. Peter Safar, 1974
Task Force of the American College of
Critical Care Medicine

Practice parameter: Hemodynamic support of patients in sepsis.

Crit Care Med 1999; 27: 639-60

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The New England Journal of Medicine

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP

November 8, 2001
Changing the Landscape
Systems Approach To Poor Sepsis Care
A Composite of Multiple Studies

- Recognition of poor sepsis care in the US ED’s
- Early Recognition (SIRS) + Risk Stratification (Lactate)
- **Sepsis Alert**
  - Cultures, Antibiotics and Source Control
- Recognition of Global Tissue Hypoxia and Cryptic Shock
- Hemodynamic Optimization Strategies
- Continuous Quality Sepsis Improvement
Saving patients from sepsis is a race against time. CDC calls sepsis a medical emergency; encourages prompt action for prevention, early recognition.

Tuesday, August 23, 2016, 1:00 p.m. ET

https://www.youtube.com/watch?v=pRtwfsTIR9s
Improved Usual-Standard Care
SIRS Cultures Antibiotics Lactate Screening Fluid Challenge Re-assessment Early ICU Admission
The Outcome Evidence of Early Sepsis Care
Results From State to National Health Care Policy
• Nearly 50,000 patients with sepsis treated at 149 New York hospitals.

• Compliance with early intravenous, fluids, antibiotics, and other elements of the early-resuscitation bundle increased from 41.5% to 55.2%.

• Mortality fell from 30.2% to 25.4%.

• Decreased hospital LOS, Levy, 2018.
Appendix Table 8: Probabilities and odds ratios of in-hospital mortality based on separate logistic regression models containing the compliance risk factor along with each of the variables in the risk adjusted model for hospital mortality developed through collaboration with the State of New York.

<table>
<thead>
<tr>
<th>Compliance risk factor</th>
<th>N</th>
<th>Probability of in-hospital mortality %</th>
<th>95% CI</th>
<th>OR for In-hospital mortality</th>
<th>95% CI</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>3-hour bundle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>29,134</td>
<td>29.3</td>
<td>28.8 – 29.8</td>
<td>0.73</td>
<td>0.70 – 0.76</td>
<td>&lt; 0.001</td>
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<tr>
<td>Yes</td>
<td>44,996</td>
<td>24.2</td>
<td>23.9 – 24.6</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6-hour bundle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>46,390</td>
<td>27.4</td>
<td>27.1 – 27.8</td>
<td>0.74</td>
<td>0.71 – 0.77</td>
<td>&lt; 0.001</td>
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<tr>
<td>Yes</td>
<td>27,361</td>
<td>22.8</td>
<td>22.3 – 23.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate reported in 3 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7,721</td>
<td>30.2</td>
<td>29.3 – 31.1</td>
<td>0.76</td>
<td>0.72 – 0.81</td>
<td>&lt; 0.001</td>
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<tr>
<td>Yes</td>
<td>66,409</td>
<td>25.8</td>
<td>25.5 – 26.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood cultures obtained prior to antibiotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>18,179</td>
<td>30.2</td>
<td>29.6 – 30.8</td>
<td>0.72</td>
<td>0.69 – 0.75</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>55,951</td>
<td>24.9</td>
<td>24.6 – 25.3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Antibiotics started in 3 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>11,448</td>
<td>29.7</td>
<td>28.9 – 30.4</td>
<td>0.78</td>
<td>0.74 – 0.82</td>
<td>&lt; 0.001</td>
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<tr>
<td>Yes</td>
<td>62,682</td>
<td>25.7</td>
<td>25.3 – 26.0</td>
<td></td>
<td></td>
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<tr>
<td>Adequate fluids in hypotensive or elevated lactate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>24,052</td>
<td>32.1</td>
<td>31.6 – 32.7</td>
<td>0.79</td>
<td>0.76 – 0.83</td>
<td>&lt; 0.001</td>
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<tr>
<td>Yes</td>
<td>27,855</td>
<td>28.1</td>
<td>27.6 – 28.6</td>
<td></td>
<td></td>
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<tr>
<td>Vasopressors if refractory hypotension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>12,449</td>
<td>38.2</td>
<td>37.4 – 39.0</td>
<td>1.03</td>
<td>0.97 – 1.10</td>
<td>0.32</td>
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<tr>
<td>Yes</td>
<td>12,145</td>
<td>38.8</td>
<td>38.0 – 39.6</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lactate re-ordered if missing or elevated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9,893</td>
<td>40.0</td>
<td>39.1 – 40.9</td>
<td>0.77</td>
<td>0.72 – 0.82</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>12,979</td>
<td>35.0</td>
<td>34.3 – 35.8</td>
<td></td>
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</tr>
</tbody>
</table>

"A SINGLE ARROW IS EASILY BROKEN, BUT NOT TEN IN A BUNDLE."

CHINESE PROVERB
There is still much work to do!
Two Decades of Diminishing Mortality

- Septic Shock: 35-38%
- Severe Sepsis: 25-30%

Mortality during or within one week of hospital discharge
Mortality during or within six months of hospital discharge
Mortality during or within one year of hospital discharge
Mortality during or within three years of hospital discharge
Inflammatory Phenotypes
Guiding Therapy: Revisiting Previous Therapies
Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: A phase III, randomized, double-blind, placebo-controlled, multicenter trial

Steven M. Opal, MD; Charles J. Fisher, Jr, MD, FCCM; Jean-François A. Dhainaut, MD, PhD; Jean-Louis Vincent, MD, PhD, FCCM; Rainer Brase, MD; Stephen F. Lowry, MD; Jerald C. Sadoff, MD; Gus J. Slotman, MD, FCCM; Howard Levy, MD; Robert A. Balk, MD, FCCM; Maire P. Shelly, FRCA; John P. Pribble, PharmD; John F. Labrecque, PhD; Janice Lookabaugh, MPH; Hugh Donovan, BS; Howard Dubin, MD, FCCM; Robert Baughman, MD; James Norman, MD; Eric DeMaria, MD; Klaus Matzel, MD; Edward Abraham, MD, FCCM; Michael Seneff, MD; The Interleukin-1 Receptor Antagonist Sepsis Investigator Group

**Conclusions:** A 72-hr, continuous intravenous infusion of rhIL-1ra failed to demonstrate a statistically significant reduction in mortality when compared with standard therapy in this multicenter clinical trial. If rhIL-1ra treatment has any therapeutic activity in severe sepsis, the incremental benefits are small and will be difficult to demonstrate in a patient population as defined by this clinical trial. (Crit Care Med 1997; 25:1115-1124)
Table 1. Inclusion criteria for the interleukin-1 receptor antagonist trial in severe sepsis

1. Clinical evidence of infection, as suggested by, but not limited to, the presence of one or more of the following signs within the previous 72 hrs
   a. Presence of polymorphonuclear cells in a normally sterile body fluid
   b. Culture or Gram stain of blood, sputum, urine, or normally sterile body fluid is positive for a pathogenic microorganism
   c. Chest radiograph is consistent with a diagnosis of pneumonia
   d. Focus of infection is identified by visual inspection (e.g., ruptured bowel with the presence of free air or bowel contents in the abdomen found at the time of surgery; wound with purulent drainage; radiographic or computed tomography evidence of an abscess or osteomyelitis; etc.)
   e. Patient has an underlying disease or condition that is likely to be associated with infection (e.g., ascending cholangitis, ischemic bowel, etc.)

2. Evidence of a systemic response to infection, as defined by the presence of all of the following signs within the previous 24 hrs
   a. Fever or hypothermia (core temperature of $\geq 38.0^\circ C$ [$\geq 100.4^\circ F$] or $\leq 36.0^\circ C$ [$\leq 96.8^\circ F$])
   b. Tachycardia (HR of $\geq 90$ beats/min), except in patients receiving a $\beta$-adrenergic receptor blocking agent or with a rate control pacemaker
   c. Tachypnea (RR of $\geq 20$ breaths/min while spontaneously breathing) or patient requires mechanical ventilation
It is also possible that this cytokine inhibitor has significant therapeutic actions, but that this activity cannot be convincingly demonstrated with this clinical trial design. Human sepsis is a complex, dynamic, and heterogeneous clinical syndrome that is difficult to accurately recognize in its early stages (21–28). The inability to define accurately a discriminatory patient population for sepsis trials remains the principal impediment to further progress in the field of sepsis research. The ideal patient population would be those patients with reversible physiologic derangements at the early phases of the cytokine-mediated, systemic inflammatory response syndrome (13). Patients who have potential major morbidity or mortality primarily attributable to sepsis would be the optimal study population for sepsis trials (22).
Review Article

EARLY BIOMARKER ACTIVITY IN SEVERE SEPSIS AND SEPTIC SHOCK AND A CONTEMPORARY REVIEW OF IMMUNOTHERAPY TRIALS: NOT A TIME TO GIVE UP, BUT TO GIVE IT EARLIER

Emanuel P. Rivers,* Anja Kathrin Jaehne,* H. Bryant Nguyen,† Demosthenes G. Papamatheakis,‡ Daniel Singer,§ James J. Yang,‖ Samantha Brown,* and Howard Klausner*

*Department of Emergency Medicine and Surgery, Henry Ford Hospital, Detroit, MI; †Departments of Emergency Medicine and Medicine, Critical Care, Loma Linda University, Loma Linda; and ‡Division of Pulmonary and Critical Care, University of California, San Diego, CA; †Department of Emergency Medicine, Mount Sinai School of Medicine, New York, NY; and ‖Department of Biostatistics and Epidemiology, Henry Ford Hospital, Detroit, Michigan

Hospital Arrival

3 hours 6 hours 12 hours 24 hours 36 hours 48-72 hours
- Peak concentration at 3 hours.
- Enrollment window up to 24 hours after onset.
- Drug be g infusion after the window of maximal biomarker activity.

The Futures of Diagnostics

• Multiple markers define disease and transitions more comprehensively.

• Multi-marker panels can aid in differential diagnosis and better define therapy.
Importance of Early Diagnosis and Clinical Care

- Early Detection and Risk Stratification
- Appropriate Disposition
- Early and Rapid Intervention: Hemodynamic and Inflammatory Phenotypes
- QA Measures: Improved Outcomes